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II. Rejection of Claims 1-3 and 5-7 Under 35 U.S.C. § 101

The Action first rejects claims 1-3 and 5-7 under 35 U.S.C. § 101, as allegedly lacking a patentable utility. Applicants respectfully traverse.

As noted by Applicants in the response filed on August 18, 2003 (“the previous response”) to the First Official Action in this case, which was mailed on May 16, 2003 (“the First Action”), the Examiner has pointed out in the that the presently claimed sequence shares **100% identity at the amino acid level** with a sequence that is present in the leading scientific repository for biological sequence data (GenBank), which has been annotated by independent third party scientists *wholly unaffiliated with Applicants* as Nit2 (alignment provided in **Exhibit A**), a nitrilase protein that interacts with the well-known tumor suppressor protein Fhit (Pace *et al.*, *Curr. Biol.* **10**:907-917, 2000). The legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. Given this GenBank annotation, there can be no question that those skilled in the art would clearly believe that Applicants’ sequence is a human nitrilase protein, exactly as asserted by Applicants in the specification as originally filed. Furthermore, given the interaction of Nit2 with a well-known tumor suppressor protein, those of skill in the art would readily recognize that the claimed sequence has a role in cancer, exactly as asserted by Applicants in the specification as originally filed (at least at page 1, line 29), and therefore, would have numerous uses, including those detailed below. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

The Examiner states that “the credibility of the asserted utility is not at issue here - instead it is the examiner’s position that the specification provides no specific and substantial asserted utility for the claimed invention” (the Action at page 2). The Examiner then states that “the specification does not assign a function to the polypeptide of SEQ ID NO:2” (the Action at page 2), but that “(i)nstead, the specification merely indicates that SEQ ID NO:2 shares an undisclosed level of structural similarity to nitrilase proteins from other organisms - this is not an assertion of function and, as such, the examiner has not interpreted this statement as such” (the Action at page 3). This statement is **completely** at odds with the Examiner’s own position in the First Action, in which he objected to the title of the application as originally filed as not descriptive, and then **specifically** suggested that the title be changed to “Nucleic Acid Encoding A Human Nitrilase Polypeptide” (the First Action at page 3). Thus, the Examiner **himself** clearly understands that the specification as originally filed does in fact “assign a function to the polypeptide of SEQ ID NO:2”. Therefore, the Examiner’s argument that “the

specification does not assign a function to the polypeptide of SEQ ID NO:2” is **completely** without merit, and in **no way** supports the allegation that the presently claimed invention lacks a patentable utility.

The Examiner states that “applicants are invited to demonstrate evidence that the specification asserts SEQ ID NO:2 has nitrilase function” (the Action at page 3). Although not required, for the reasons set forth above, Applicants respectfully point out that, in addition to the statement from the specification as originally filed detailed above, the specification states that the presently described sequences are “nitrilase-like” (at least at page 2, line 31). The Examiner seems to be requiring an example in the specification as originally filed demonstrating that the presently claimed sequence has nitrilase activity. However, this position as applied to the presently claimed sequences is wholly unsupported by mandatory legal precedent, for it has long been established that “there is no statutory requirement for the disclosure of a specific example”. *In re Gay*, 309 F.2d 769, 135 USPQ 311 (CCPA, 1962).

Thus, the present situation appears to track Example 10 of the Revised Interim Utility Guidelines Training Materials (pages 53-55; **Exhibit B**), which **clearly** establishes that a rejection under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility (see Section III, below), is not proper when a full length sequence (such as the presently claimed sequences) has a similarity score greater than 95% to a protein having a known function (such as the **100% identity** between SEQ ID NO:2 and Nit2, as discussed above). Therefore, the United States Patent and Trademark Office’s **own** examination guidelines **clearly** indicate that the present claims meet the requirements of 35 U.S.C. § 101, and the rejection of record should be withdrawn.

The Examiner then states that “this reference [*Pace et al.*] was not available to one of ordinary skill in the art at the time of the invention” (the Action at page 3). While this statement is **totally** obvious, since had “this reference” been “available to one of ordinary skill in the art at the time of the invention”, “this reference” would have anticipated the presently claimed invention, Applicants respectfully point out that this fact is **completely and totally irrelevant** with regard to the **utility** issue at hand. Applicants point to the *Pace et al.* reference, **not** to evidence that the presently claimed sequence was known in the art at the time the present application was filed, but, rather, to evidence that other skilled artisans have **confirmed** the involvement of the presently claimed sequence in cancer, exactly as set forth by Applicants in the specification as originally filed (at least at page 1, line 29).

Thus, this argument by the Examiner also in no way supports the alleged lack of utility.

The Examiner then states that “further experimentation would have been required to confirm such a hypothesis”, and thus “this disclosure alone - without further experimentation - is insufficient to establish a utility for the claimed invention” (the Action at page 3). These are just the first two times in the Action (out of a total of at least eight times) that the Examiner alleges that the presently claimed invention lacks a patentable utility because “further experimentation” (the Action at pages 4, 6, 7 and 8) or “additional experimentation” (the Action at pages 5 and 6) would be required in certain aspects of the invention. Applicants respectfully point out that the standard for meeting the requirements of 35 U.S.C. § 101 is not whether “further” experimentation or “additional” experimentation is required to practice the claimed invention, but whether “undue” experimentation would be required to practice the claimed invention. The widespread knowledge of the interaction between the well-known tumor suppressor Fhit and members of the nitrilase family in invertebrates, along with the extensive similarities between Fhit and the nitrilase family between invertebrates and mammals, strongly argues against such a use requiring “undue experimentation”. Importantly, in assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is “undue”, not “experimentation”. *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra; Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988; “*Wands*”). Thus, the Examiner’s argument does not support the alleged lack of utility, and the present claims clearly meet the requirements of 35 U.S.C. § 101.

Therefore, as pointed out by Applicants in the previous response, given the likely involvement of the presently claimed sequence in cancer, as just one example of the utility of the present nucleotide sequences, the skilled artisan would readily appreciate the utility of tracking expression of the presently claimed sequence. The specification details, at least at page 5, lines 18-20, that the present nucleotide sequences have utility in assessing gene expression patterns using high-throughput DNA chips. Such “DNA chips” clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776 (**Exhibits C-H**; copies of issued U.S. Patents not provided pursuant to current United States Patent

and Trademark Office policy). As the present sequences are specific markers of human chromosome 3 (see below), and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such DNA chips. Given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful.

Further evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company (Rosetta Inpharmatics) was viewed to have such "real world" value that it was acquired by large a pharmaceutical company (Merck) for significant sums of money (net equity value of the transaction was \$620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, *Science* **291**:1304, 2001; **Exhibit I**). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, *Science* **291**:1153, 2001; **Exhibit J**). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years). Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

The Examiner questions this utility because "there is no evidence in the specification that indicates that SEQ ID NO:1 or SEQ ID NO:2 are involved in cancer" (the Action at page 3). However, as set forth above, the specification as originally filed does detail the involvement of the presently claimed sequence in cancer (at least at page 1, line 29). Thus, this argument by the Examiner

also in no way supports the alleged lack of utility. The Examiner seems to be requiring an example in the specification as originally filed demonstrating that the presently claimed sequence has a role in cancer. However, as set forth above, for it has long been established that “there is no statutory requirement for the disclosure of a specific example”. *In re Gay, supra*. As pointed out above, the widespread knowledge of the interaction between the well-known tumor suppressor Fhit and members of the nitrilase family in invertebrates, along with the extensive similarities between Fhit and the nitrilase family between invertebrates and mammals, **strongly** argues that the skilled artisan would believe that the presently claimed sequence is involved in cancer. Thus, the Examiner’s argument once again does not support the alleged lack of utility, and the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Examiner further questions this asserted utility, stating that “any sequence can be included as a component of a gene chip” (Action at page 4). As pointed out by Applicants in the previous response, this argument is flawed in **at least** two respects. First, the asserted utility is in assessing **gene expression patterns** using high-throughput DNA chips. Applicants reiterate that only **expressed** sequences can be used to track gene expression, not just **any** nucleic acid. Expression profiling does not require a knowledge of the function of the particular nucleic acid on the chip - rather the gene chip indicates which DNA fragments are expressed at greater or lesser levels in two or more particular tissue types, such as cancer cell lines and normal controls. Skilled artisans already **have used** and **continue to use** sequences such as Applicants in gene chip applications **without** further experimentation. Second, the Examiner is still clearly confusing the requirements of a **specific** utility, which is the **proper** standard for utility under 35 U.S.C. § 101, with the requirement for a **unique** utility, which is clearly an **improper** standard. As clearly set forth by the Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991):

An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: “[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility.” *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

Following directly from the quote above, an invention does not need to be the **best** or **only** way to accomplish a certain result. Thus, the question of whether or not **other** nucleic acid sequences can be used to assess gene expression patterns using DNA chips is **completely irrelevant** to the present utility inquiry. The **only** relevant question in regard to meeting the standards of 35 U.S.C. § 101 is whether **every** nucleic acid can be so used - and the clear answer to this question is an emphatic **no**.

Importantly, the holding in *Carl Zeiss* is **mandatory legal authority** that essentially controls the outcome of the present case. This case, and particularly the cited quote, **directly** rebuts the Examiner's argument. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Furthermore, Applicants pointed out in the previous response that the requirement for a unique utility is clearly not the standard adopted by the Patent and Trademark Office. If every invention were required to have a unique utility, the Patent and Trademark Office would no longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human diseases, such as cancer, just to name a few particular examples, because the utility of each of these compositions is applicable to the broad class in which each of these compositions falls: all batteries have the same utility, specifically to provide electrical power; all automobile tires have the same utility, specifically for use on automobiles; all golf balls and golf clubs have the same utility, specifically for use in the game of golf; and all cancer treatments have the same utility, specifically, to treat cancer. However, only the briefest perusal of virtually any issue of the Official Gazette provides numerous examples of patents being granted on each of the above compositions nearly **every week**. Furthermore, if a composition needed to be unique to be patented, the entire class and subclass system would be an effort in futility, as the class and subclass system serves solely to group such common inventions, which would not be required if each invention needed to have a **unique** utility. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

The Examiner states that “applicants mischaracterize the examiner’s position as applicants have been required to identify a utility that is **specific** to the invention claimed, as opposed to one that would apply regardless of the specific properties of the claimed invention” (the Action at page 5, emphasis in original). The Examiner appears to be requiring a specific technical feature for the present invention, which, while an entirely proper requirement for certain **foreign** patent applications, is **not at all germane** to the question of the utility of the present **United States** patent application. Applicants reiterate that the requirement for a **unique** utility is **not** the proper standard under 35 U.S.C. § 101. Every battery has the exact same **specific** utility, specifically to provide electrical power; every automobile tire has the exact same **specific** utility, specifically for use on automobiles; every golf ball and golf club has the exact same **specific** utility, specifically for use in the game of golf. Thus, based on the relevant legal standard, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

The Examiner further questions this asserted utility, stating that “any information derived from gene expression analysis using the claimed sequences would be meaningless as the specification fails

to provide guidance for interpreting any result obtained thereby” (The Action at page 4). Applicants respectfully submit that the skilled artisan would readily understand the meaning of the results “derived from gene expression analysis using the claimed sequences”. For example, if the claimed sequence was found to be expressed at higher levels in cancer tissue, given the well-established interaction between the tumor suppressor Fhit and Nit2, the skilled artisan would immediately understand that the presently claimed sequence has a direct role in that particular cancer tissue. The fact that there is an **entire, multimillion dollar industry** established based on the use of gene sequences or fragments thereof in a gene chip format, supports Applicants position that those of skill in the art do not need “guidance for interpreting any result obtained thereby”. Applicants once again point out that, as a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands, supra*. Thus, the Examiner’s argument once again does not support the alleged lack of utility, and the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Examiner then erroneously states that “(e)vidence of commercial success, while sometimes persuasive as secondary evidence of non-obviousness, is immaterial to utility and enablement” (the Action at page 4). This could not be **further** from the truth. The Examiner repeatedly alleges that the presently claimed invention does not have a “‘real world’ context of use” (the First Action at page 4), and that the presently claimed invention is not useful “in currently available form” (the Action at page 5). The evidence of commercial success **directly** rebuts the Examiner’s allegation that the presently claimed sequences do not have a “‘real world’ context of use” and is not useful “in currently available form”, unless it is the position of the Examiner that the entire gene chip industry does not exist in the “real world”. Thus, “applicants’ own statement regarding the widespread use of such gene chips using public domain gene sequences” is **not**, as **completely mischaracterized** by the Examiner, evidence that “any sequence can be included as a component of a gene chip” (Action at page 4), but, rather, **direct** evidence that the presently claimed sequence is in fact useful “in currently available form”. Therefore, the Examiner’s argument is **completely** without merit, and in **no way** supports the allegation that the presently claimed invention lacks a patentable utility.

Next, the Examiner states that “(a)ny **expressed** or **non-expressed** sequence can be used for gene expression monitoring” (the Action at page 5, emphasis in original). Applicants hardly know where to begin. It is completely beyond all bounds of logic that “any ... **non-expressed** sequence can be used for gene expression monitoring”. **By definition**, non-expressed sequences are **not expressed**, and thus **cannot** be used to monitor gene **expression**. The Examiner is requested to

provide evidence that “any ... non-expressed sequence can be used for gene expression monitoring”, in order to support this position. Absent such evidence, the Examiner’s argument is completely without merit, and in no way supports the allegation that the presently claimed invention lacks a patentable utility.

As set forth in the previous response, although Applicants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), as a further example of the utility of the presently claimed polynucleotide, as described in the specification at least at page 10, line 25, the present nucleotide sequence has a specific utility in “determining the genomic structure” of the gene encoding the presently claimed sequences, for example mapping the protein encoding regions. This is evidenced by the fact that SEQ ID NO:1 can be used to map the 9 coding exons on chromosome 3 (present within the chromosome 3 clone, GenBank Accession Number AC093003; alignment and first page of the GenBank report are shown in **Exhibit K**). Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of human chromosome 3 that contains the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence. For further evidence in support of the Applicants’ position, the Examiner is requested to review, for example, section 3 of Venter *et al.* (*supra*, at pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Action once again questions this utility, again stating that “any human polynucleotide which (*sic*) encodes a protein can be used to determine the specific chromosome which (*sic*) contains that locus” (the Action at page 5). First, Applicants once again remind the Examiner that only a minor

percentage (2-4%) of the genome actually encodes exons, which in-turn encode amino acid sequences. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). It is well-known that exon splice junctions can often be hot spots for erroneous events leading to cancer. The claimed sequences identify biologically verified exon splice junctions, as opposed to splice junctions that may have been bioinformatically predicted from genomic sequence alone. The specification also details that “sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (*e.g.*, splice acceptor and/or donor sites), *etc.*, that can be used in diagnostics and pharmacogenomics” (specification at page 10, lines 26-31). Applicants respectfully submit that the practical scientific value of biologically validated, expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Second, the Examiner is once again confusing the requirements of a specific utility, which is the proper standard for utility under 35 U.S.C. § 101, with the requirement for a unique utility, which is clearly an improper standard. The fact that a small number of other nucleotide sequences could be used to map the protein coding regions in this specific region of chromosome 3 does not mean that the use of Applicants’ sequence to map the protein coding regions of chromosome 3 is not a specific utility (*Carl Zeiss Stiftung v. Renishaw PLC, supra*; “[A]n invention need not be the best or only way to accomplish a certain result”). The holding in *Carl Zeiss*, and particularly the quote provided above, clearly states that an invention does not need to be the only way to accomplish a certain result. Applicants reiterate that the question of whether or not other nucleic acid sequences “can be used to determine the specific chromosome which (*sic*) contains that locus” is completely irrelevant to the present utility inquiry. The only relevant question in regard to meeting the standards of 35 U.S.C. § 101 is whether every nucleic acid can be so used - and the clear answer to this question is once again an emphatic no. Applicants reiterate that the holding in *Carl Zeiss* is mandatory legal authority that essentially controls the outcome of the present case. This case, and particularly the cited quote, directly rebuts the Examiner’s argument. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

It is important to note that it has been clearly established that a statement of utility in a

specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974; “*Langer*”); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971). As clearly set forth in *Langer*:

As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

Langer at 297, emphasis in original. As set forth in the MPEP, “Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered ‘false’ by a person of ordinary skill in the art” (MPEP, Eighth Edition at 2100-40, emphasis added). Absent such evidence from the Examiner, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Rather, as set forth by the Federal Circuit, “(t)he threshold of utility is not high: An invention is ‘useful’ under section 101 if it is capable of providing some identifiable benefit.” *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that “(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result.” *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985); “*Cross*”) states “any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101”. *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that “anything under the sun that is made by man” is patentable (*State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)).

The Examiner seems to discount the case law cited by Applicants, stating “(i)n *Juicy Whip Inc. v. Orange Bang Inc.*, the issue of utility was discussed in regard to a juice dispenser, in *Brooktree Corp. v. Advanced Micro Devices, Inc.*, the issue of utility was discussed in regard to digital analog conversion circuitry, and in *State Street Bank & Trust Co. v. Signature Financial Group Inc.*, the issue of utility was discussed in regard to a business method” (the Action at page 7). Applicants respectfully point out that the holding in these cases is mandatory legal authority, and that the Examiner must follow the precedent as applied to the broad issue at hand in each cited case, unless a case is specifically limited to it's facts by the Court itself. Furthermore, Section 101 of the Patent Act of 1952, 35 U.S.C. § 101, provides that “[w]hoever invents or discovers any new and useful

process, machine, manufacture, or composition of matter, or any new and useful improvement thereof," may obtain a patent on the invention or discovery. Applicants point out that 35 U.S.C. § 101 covers devices (machines) as well as compositions, and makes no distinction between the two with regard to meeting the burden of complying with 35 U.S.C. § 101. Additionally, *Juicy Whip Inc. v. Orange Bang Inc.* cites *Brenner v. Manson*, 383 U.S. 519 (1966), which the Examiner obviously believes is relevant to the present case, since the Examiner himself cited this exact case in the First Action (the First Action at page 4). Also, *Diamond vs. Chakrabarty*, *supra*, specifically concern compositions. Thus, this argument is completely improper, and totally fails to support the alleged lack of utility of the presently claimed compositions.

The Examiner then states that "in contrast to *Cross v. Iizuka*, the claimed invention fails to benefit the public in currently available form" (the Action at page 8). However, as discussed at length, above, the widespread use of nucleotide sequences such as Applicants in numerous applications, from assessing gene expression patterns using gene chips to mapping the protein coding regions of chromosomes, is direct evidence that the claimed invention in fact does "benefit the public in currently available form". Therefore, the Examiner's argument is completely without merit, and in no way supports the allegation that the presently claimed invention lacks a patentable utility.

In *In re Brana*, (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*"), the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well

before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted. The Action states that “it should be noted that no further experimentation was required” in *Brana* (the Action at page 8, emphasis in original). Applicants reiterate that even if, *arguendo*, further research might be required in certain aspects of the present invention, this does not preclude a finding that the invention has utility, as set forth by the Federal Circuit’s holding in *Brana*, which clearly states, as highlighted in the quote above, that “pharmaceutical inventions, necessarily includes the expectation of further research and development” (*Brana* at 1442-1443, emphasis added). Furthermore, as detailed at length above, the standard for meeting the requirements of 35 U.S.C. § 101 is not whether “further” experimentation or “additional” experimentation is required to practice the claimed invention, but whether “undue” experimentation would be required to practice the claimed invention. Once again, in assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is “undue”, not “experimentation” (*In re Angstadt and Griffin, supra*). Additionally, the need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd., supra*. Thus, the Examiner’s argument once again does not support the alleged lack of utility, and the present claims clearly meet the requirements of 35 U.S.C. § 101.

Finally, Applicants pointed out in the previous response that the requirements set forth in the Action for compliance with 35 U.S.C. § 101 do not comply with the requirements set forth by the Patent and Trademark Office (“the PTO”) itself for compliance with 35 U.S.C. § 101. While Applicants are well aware of the new Utility Guidelines set forth by the USPTO, Applicants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Applicants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have

been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Examiner is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,281 (each of which claims short polynucleotides; **Exhibits L-N**; copies of issued U.S. Patents not provided pursuant to current United States Patent and Trademark Office policy), and recently issued U.S. Patent No. 6,340,583 (which includes no working examples; **Exhibit O**; copies of issued U.S. Patents not provided pursuant to current United States Patent and Trademark Office policy), none of which contain examples of the “real-world” utilities that the Examiner seems to be requiring. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section III, below), Applicants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Applicants understand that each application is examined on its own merits, Applicants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Thus, holding Applicants to a different standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

The Examiner states that “the guidelines were promulgated by the PTO in accordance with all applicable case law” (the Final Action at page 3). Unfortunately, as discussed at length above, this is simply **not true**. Applicants have noted numerous cases that directly contradict the PTO’s new utility guidelines, and are unaware of any Federal Circuit or Supreme Court decisions to date that have examined, let alone validated, the current utility guidelines. And while Applicants understand that the PTO is bound to follow their own guidelines, until a definitive ruling by the Federal Circuit or the Supreme Court, these guidelines should not be confused in **any way** with the force of law. There are numerous examples over the years of USPTO guidelines that have been found not to comport with the patent laws and rules. As just one example of the Federal Circuit overturning guidelines enacted *sua sponte* by the USPTO, the Examiner is invited to review *In re Brana, supra*. Thus, this argument also fails to support the alleged lack of utility.

For each of the foregoing reasons, as well as the reasons set forth in the previous response, which are incorporated herein in their entirety by reference, Applicants submit that as the presently claimed nucleic acid molecules have been shown to have a substantial, specific, credible and

well-established utility, the rejection of claims 1-3 and 5-7 under 35 U.S.C. § 101 has been overcome, and request that the rejection be withdrawn.

III. Rejection of Claims 1-3 and 5-7 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1-3 and 5-7 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse.

Applicants submit that as claims 1-3 and 5-7 have been shown to have “a specific, substantial, and credible utility”, as detailed in section II above, the present rejection of claims 1-3 and 5-7 under 35 U.S.C. § 112, first paragraph, cannot stand.

Applicants therefore request that the rejection of claims 1-3 and 5-7 under 35 U.S.C. § 112, first paragraph, be withdrawn.

IV. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Steadman have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

March 10, 2004

Date



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CUSTOMER NUMBER: 24231



020202 ACCESSION:NM_020202 NID: gi 31543290 ref NM_020202.2
Homo sapiens Nit protein 2 (NIT2), mRNA
Length = 1019

Score = 564 bits (1438), Expect = e-158
Identities = 276/276 (100%), Positives = 276/276 (100%)
Frame = +2

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IVYSDIDLKKLAEIRQQIPVFRQKRSDLYAVEMKKP
Sbjct: 794 IVYSDIDLKKLAEIRQQIPVFRQKRSDLYAVEMKKP 901

AF284574 ACCESSION:AF284574 NID: gi 9367115 gb AF284574.1 AF284574
Homo sapiens Nit protein 2 (NIT2) mRNA, complete cds
Length = 962

Score = 564 bits (1438), Expect = e-158
Identities = 276/276 (100%), Positives = 276/276 (100%)
Frame = +1

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Query: 121 PGKITFQESKTLSPGDSFSTFDTPYCRVGLGICYDMRFAELAQIYAQRGCQLLVYPGAFN 180
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characterize the protein. A starting material that can only be used to produce a final product does not have a substantial asserted utility in those instances where the final product is not supported by a specific and substantial utility. In this case none of the proteins that are to be produced as final products resulting from processes involving the claimed cDNA have asserted or identified specific and substantial utilities. The research contemplated by Applicants to characterize potential protein products, especially their biological activities, does not constitute a specific and substantial utility. Identifying and studying the properties of the protein itself or the mechanisms in which the protein is involved does not define a "real world" context of use. Note, because the claimed invention is not supported by a specific and substantial asserted utility for the reasons set forth above, credibility has not been assessed. Neither the specification as filed nor any art of record discloses or suggests any property or activity for the cDNA compounds such that another non-asserted utility would be well established for the compounds.

Claim 1 is also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.

Example 10: DNA Fragment encoding a Full Open Reading Frame (ORF)

Specification: The specification discloses that a cDNA library was prepared from human kidney epithelial cells and 5000 members of this library were

sequenced and open reading frames were identified. The specification discloses a Table that indicates that one member of the library having SEQ ID NO: 2 has a high level of homology to a DNA ligase. The specification teaches that this complete ORF (SEQ ID NO: 2) encodes SEQ ID NO: 3. An alignment of SEQ ID NO: 3 with known amino acid sequences of DNA ligases indicates that there is a high level of sequence conservation between the various known ligases. The overall level of sequence similarity between SEQ ID NO: 3 and the consensus sequence of the known DNA ligases that are presented in the specification reveals a similarity score of 95%. A search of the prior art confirms that SEQ ID NO: 2 has high homology to DNA Ligase encoding nucleic acids and that the next highest level of homology is to alpha-actin. However, the latter homology is only 50%. Based on the sequence homologies, the specification asserts that SEQ ID NO: 2 encodes a DNA ligase.

Claim 1: An isolated and purified nucleic acid comprising SEQ ID NO: 2.

Analysis: The following analysis includes the questions that need to be asked according to the guidelines and the answers to those questions based on the above facts:

1) Based on the record, is there a "well established utility" for the claimed invention? Based upon applicant's disclosure and the results of the PTO search, there is no reason to doubt the assertion that SEQ ID NO: 2 encodes a DNA ligase. Further, DNA ligases have a well-established use in the molecular biology art based on this class of protein's ability to ligate DNA. Consequently the answer to the question is yes.

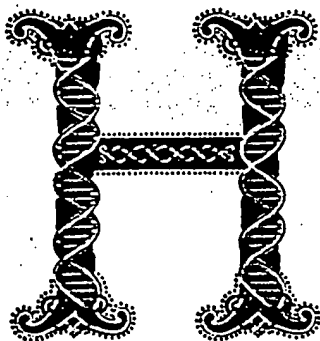
Note that if there is a well-established utility already associated with the claimed invention, the utility need not be asserted in the specification as filed. In order to determine whether the claimed invention has a well-established utility the examiner must determine that the invention has a specific, substantial and credible utility that would have been readily apparent to one of skill in the art. In this case SEQ ID NO: 2 was shown to encode a DNA ligase that the artisan would have recognized as having a specific, substantial and credible utility based on its enzymatic activity.

Thus, the conclusion reached from this analysis is that a 35 U.S.C. § 101 rejection and a 35 U.S.C. § 112, first paragraph, utility rejection should not be made.

Example 11: Animals with Uncharacterized Human Genes

Specification: Kidney cells from a patient with Polycystic Kidney (PCK) Disease have been used to make a cDNA library. From this library 8000 nucleotide "fragments" have been sequenced but not yet used to express proteins in a transformed host cell nor have they been characterized in any other way. The 50 longest fragments, SEQ ID NO: 1-50, respectively, have been used to make transgenic mice. None of the 50 lines of mice have developed Polycystic Kidney Disease to date. The asserted utility is the use of the mice to research human genes from diseased human kidneys. The disease is inheritable, but chromosomal loci have not yet been identified. Neither the absence or presence of a specific protein has been identified with the disease condition.

THE HUMAN GENOME



umanity has been given a great gift. With the completion of the human genome sequence, we have received a powerful tool for unlocking the secrets of our genetic heritage and for finding our place among the other participants in the adventure of life.

This week's issue of *Science* contains the report of the sequencing of the human genome from a group of authors led by Craig Venter of Celera Genomics. The report of the sequencing of the human genome from the publicly funded consortium of laboratories led by Francis Collins appears in this week's *Nature*. This stunning achievement has been portrayed—often unfairly—as a competition between two

ventures, one public and one private. That characterization detracts from the awesome accomplishment jointly unveiled this week. In truth, each project contributed to the other. The inspired vision that launched the publicly funded project roughly 10 years ago reflected, and now rewards, the confidence of those who believe that the pursuit of large-scale fundamental problems in the life sciences is in the national interest. The technical innovation and drive of Craig Venter and his colleagues made it possible to celebrate this accomplishment far sooner than was believed possible. Thus, we can salute what has become, in the end, not a contest but a marriage (perhaps encouraged by shotgun) between public funding and private entrepreneurship.

There are excellent scientific reasons for applauding an outcome that has given us two winners. Two sequences are better than one; the opportunity for comparison and convergence is invaluable. Indeed, a real-world proof of the importance of access to both sets of data can be found in the pages of this issue of *Science*, in the comparative analysis by Olivier *et al.* (p. 1298).

Although we have made the point before, it is worth repeating that the sequencing of the human genome represents, not an ending, but the beginning of a new approach to biology. As Galas says in his Viewpoint (p. 1257), the knowledge that all of the genetic components of any process can be identified will give extraordinary new power to scientists. Because of this breakthrough, research can evolve from analyzing the effects of individual genes to a more integrated view that examines whole ensembles of genes as they interact to form a living human being. Several articles in this issue highlight how this approach is already beginning to revolutionize the way we look at human disease.

This has been a massive project, on a scale unparalleled in the history of biology, but of course it has built on the scientific insights of centuries of investigators. By coincidence, this landmark announcement falls during the week of the anniversary of the birth of Charles Darwin. Darwin's message that the survival of a species can depend on its ability to evolve in the face of change is peculiarly pertinent to discussions that have gone on in the past year over access to the Celera data. (Full information regarding the agreements that were reached to make the data available can be found at www.sciencemag.org/feature/data/announcement/gsp.shl.) We are willing to be flexible in allowing data repositories other than the traditional GenBank, while insisting on access to all the data needed to verify conclusions. In this domain, change is everywhere: Commercial researchers are producing more and more potentially valuable sequences, yet (at least in the United States) laws governing databases provide scant protection against piracy. Had the Celera data been kept secret, it would have been a serious loss to the scientific community. We hope that our adaptability in the face of change will enable other proprietary data to be published after peer review, in a way that satisfies our continuing commitment to full access.

It should be no surprise that an achievement so stunning, and so carefully watched, has created new challenges for the scientific venture. *Science* is proud to have played a role in bringing this discovery onto the public stage. It is literally true that this is a historic moment for the scientific endeavor. The human genome has been called the Book of Life. Rather, it is a library, in which, with rules that encourage exploration and reward creativity, we can find many of the books that will help define us and our place in the great tapestry of life.

Barbara R. Jasny and Donald Kennedy

**A historic
moment for
the scientific
endeavor.**

Query= SEQ ID NO:1
 (831 letters)

Sequences producing significant alignments:

Score E
 (bits) Value

AC093003.11.1.153680

244 7e-62

>AC093003.11.1.153680

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Strand = Plus / Minus

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NCBI Nucleotide

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM

Search for

Limits Preview/Index History Clipboard Detail

Show:

☐ 1: AC093003. Homo sapiens 3 BA...[gi:22549642]

Link

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DEFINITION Homo sapiens 3 BAC RP11-114I8 (Roswell Park Cancer Institute Human
BAC Library) complete sequence.
ACCESSION AC093003
VERSION AC093003.11 GI:22549642
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SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (bases 1 to 153680)
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Douthwaite,K.J., Draper,H., Dugan-Rocha,S., Durbin,K.J.,
Earnhart,C., Edgar,D., Edwards,C.C., Elhaj,C., Escotto,M.,
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Gabisi,A., Gao,J., Garcia,A., Garner,T., Garza,N., Gill,R.,
Gorrell,J.H., Guevara,W., Gunaratne,P., Hale,S., Hamilton,K.,
Harris,C., Harris,K., Hart,M., Havlak,P., Hawes,A., He,X.,
Hernandez,J., Hernandez,O., Hodgson,A., Hogues,M., Holloway,C.,
Hollins,B., Homsy,F., Howard,S., Huber,J., Hulyk,S., Hume,J.,
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Joudah,S., Karlsson,E., Kelly,S., Khan,U., King,L., Korvah,J.,
Kovar,C., Kratovic,J., Kureshi,A., Landry,N., Leal,B., Lewis,L.C.,
Lewis,L., Li,J., Li,Z., Lichtarge,O., Lieu,C., Liu,J., Liu,W.,
Loulseged,H., Lozado,R.J., Lu,X., Lucier,A., Lucier,R., Luna,R.,
Ma,J., Maheshwari,M., Mapua,P., Martin,R., Martindale,A.,
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Mei,G., Metzker,M., Miner,G., Miner,Z., Mitchell,T., Mohabbat,K.,
Moore,S., Morgan,M., Moorish,T., Morris,S., Moser,M., Neal,D.,
Nelson,D., Newton,J., Newton,N., Nguyen,A., Nguyen,N., Nguyen,N.,
Nickerson,E., Nwokenkwo,S., Oguh,M., Okwuonu,G., Oragunye,N.,
Oviedo,R., Pace,A., Payton,B., Peery,J., Perez,L., Peters,L.,
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Rojas,A., Rojubokan,I., Rolfe,M., Ruiz,S., Savery,G., Scherer,S.,
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Tabor,P., Tamerisa,A., Tamerisa,K., Tang,H., Tansey,J., Taylor,C.,
Taylor,T., Telfrod,B., Thomas,N., Thomas,S., Usmani,K., Vasquez,L.,